GEN-PROBE

July 27, 2000

Food and Drug Administration
Dockets Management Branch (HFA –305)
5600 Fishers Lane - Room 1061
Rockville, MD 20857

Re: Docket No. 00N-1394 – CLIA Waiver Criteria

Dear Ms. Sliva and FDA/CLIA Staff:

On July 21, 2000, the FDA published the above referenced document and requested responses to a series of questions. For convenience of the readers, the questions have been transcribed. Responses appear in **bold**.

General Questions for Public Input

Criteria for waived tests under the Public Health Service Act were amended by FDAMA to read: waived tests "are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that -

"(A) employ methodologies that are so simple and accurate to render the likelihood of erroneous results by the user negligible, or (B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly..."

1. What criteria should be used to demonstrate that a waived test is a simple laboratory examination and procedure with "an insignificant risk of an erroneous result?" For example:
   A. Should a waived test, when performed by untrained users, provide an accurate result with no significant clinical or statistical error when compared to a measure of truth? This requires availability of well-characterized reference methods and/or materials as part of the waived test assessment. The current threshold for waiver as established by CDC is no significant inaccuracy and no significant imprecision.

Response: No, a "clinical or statistical error when compared to a measure of truth" was not the intent of Congress and, to my knowledge, has never been interpreted in that way. The measure is as follows: When a lay person performs the test, with no prior experience and no formal lab training, do they achieve the same results as a trained laboratorian? The risk of consequences must be negligible when performed by either party to have the test meet the "safety and effectiveness" standard of FDA clearance. Therefore, if the product is cleared and an untrained person can perform it with the same success as a trained person, the safety and effectiveness are

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the same. The concept of a reference method comparison is a recent invention or proposal, and should be replaced with the performance accuracy comparison study.

B. Should a waived test, when performed by untrained users, provide a test result that shows no user error when compared to the same test performed in a CLIA-certified lab by a trained user? This requires comparison of the test in a lay-user setting with performance of the test in a CLIA-certified lab by a trained user. The threshold for waiver would be no difference in performance in the two settings.

Response: The above proposal is close to correct. It goes too far to say "no user error" as perfection should not be expected in any venue. The potential for error must be small and the demonstration of the test in a controlled setting of lay vs. professional users should show very low error rates. It's possible that either the lay or professional user could make a mistake, but as long as the rate is low, this is tolerable. As precedent, note that Congress specifically listed blood glucose monitors as on the waived list. It is well known that some errors can and do occur with this technology. Therefore, it is clear that the intent of Congress is not to waive only devices that provide perfect results all the time. Instead, Congress was looking for a low error rate and for the regulating agency to weigh the public health benefit of the availability of the waived test outside laboratories regulated by moderate or highly complex CLIA rules.

C. Should FDA apply a different model to determine the waived status of a test?

Response: The model should include an assessment of public health benefit, a comparison of the accuracy of result when comparing lay vs. professional users, and should avoid any consideration of "control" of laboratory tests.

2. What criteria should FDA use to determine if a methodology is "so simple and accurate to render the likelihood of erroneous results by the user negligible?"

Response: For a test to be cleared for marketing by the FDA, it must be "safe and effective." If a lay user can provide result accuracy the same as professional users and the instructions are sufficiently clear for the lay user to understand what those results mean, the CLIA criteria are met and safety and efficacy criteria are met.

A. Should a waived test be so accurate when performed by untrained users that inaccurate results will not occur?

Response: No, see previous response.

B. Should a waived test have variable accuracy if used adjunctively; is it acceptable to waive tests that have inaccurate results but do not have any major negative clinical impact? How should FDA make this assessment?

Response: Most diagnostic tests are adjunctive. It would be very difficult to say otherwise since most of the tests under consideration would not be used alone to make a diagnosis in an asymptomatic population. An exception would be cholesterol screening. In this case, asymptomatic populations could be tested, but the results would not be likely to create a hazard in any way. The most likely result to a positive test would be to alter diet or see a physician for additional lipid profile testing. For other potential diagnostics to be waived, there should be a weighting given to the public benefit of having these tests increase their availability in physicians' offices and not assume that the purpose of the waiver submission is for someone to start Mall screenings. It is in this philosophy that the FDA must weigh the public health benefit vs. trying to keep control of lab tests in certain laboratories.

In regard to variable accuracy, the accuracy of the test should be the same whether it is performed by a laboratory professional or a lay person. If the results of correctly performed tests are variable as an inherent limitation of the test, lay labeling should explain the meaning and the clinical evaluation should test whether the lay user understands what is being provided. This should be done with either written or verbal questions and should be included in the waiver application. Although most tests would be intended for physicians' offices, a waiver may allow OTC use. The FDA could clarify this situation by requiring that the waiver be for Rx or OTC use, or both. If the waiver is for Rx use only, there's no reason anyone other than physician office staff members would need to demonstrate ability to run the test with the same success as a laboratory professional.

3. What criteria should FDA use in determining that a test will "pose no unreasonable risk of harm to the patient if performed incorrectly?"

Response: As stated in the answer above, the whole waiver category should be broken down into Rx and OTC. Then this question can be enhanced to read, "when performed in a physician's office or when performed by a patient." It should be up to the applicant to document the benefit and risk of a false negative or false positive. It will also depend on the test and the action taken when a test is a valid positive, valid negative, or false result. While Industry and the FDA prefer to write a tight guidance on this question that will fit all situations and all test venues, that would be contrary to the public health. The FDA should create a series of questions on HOW to assess potential harm. As a starting point, here are some questions:

- **Is the test to be Rx and performed by a physician, the physician's staff or under direction of a physician?**
- **Is the test to be OTC and performed by the lay public?**

This algorithm should be worked out from the perspective that there is value in having waived tests and the FDA public health goal is to minimize approval of potentially hazardous tests, but not to ban any test that is not "perfect" in it's performance.

4. Should the waiver process be different for screening tests that require a second test for confirmation? Since there are no CLIA standards for performance of waived testing, except instructions to follow the manufacturer's package insert,

   that is the assurance that confirmatory testing will be performed? Should the need for confirmatory testing raise, lower, or have no impact on the threshold for a waiver decision?

Response: Once again, this should be on a test by test basis. Following the Congressional example, specific tests were deemed important to be on the original waived list. If we were to evaluate those tests on the basis of this question, the answers would not be standard or necessarily comply with the intent of Congress. The best approach would be to examine the variability of the tests Congress waived in the beginning and allow for the same variability and consideration for new tests. To reiterate, the public health benefit vs. risk of false result is more important than simply denying the waiver based on whether or not an individual might not secure confirmatory testing.

Specific Questions for Public Input

5. Should accuracy be determined using comparison of the waiver test to a well-characterized reference method and/or materials, to a designated comparative method and/or materials, to a working laboratory method and/or materials, to a clinical algorithm for diagnosis and/or to other endpoints?

Response: None of the above. Accuracy should be compared between the lay user and the professional user. If the product has a 510(k), it's substantially equivalent to a marketed product already, and the accuracy should be the same from a lay user compared to a professional user of the same product being proposed for a waiver. Testing must be consistent with the 'Intended Use' of the product.

6. How many samples, what types of samples (real or artificial) by how many users and how many sites are appropriate to evaluate accuracy? (Current guidelines being followed by FDA are for performance to be demonstrated by laboratory users at a minimum of one site.)

Response: Since site to site reproducibility is tested during the 510(k) evaluation, it need not be repeated for a CLIA waiver application. What is important is that there are enough lay users being compared to some smaller number of professional users. Artificial samples should be fine unless there's something difficult about the sample collection. For example, for a urine test, there would be no reason to collect or use real urine for the comparison study. For a finger stick test, those tests are already waived in multiple products. Some new questions would have to come up to make the public prove again, they could collect a sample. Therefore, one site should be sufficient, but the number of testers would be up to the sponsor. If 30 lay users and three professionals were participating, and all got right answers from a series of

samples, that should be enough. If there were errors, then the statisticians would need to get involved. The best way to establish sample size would be for the sponsor to determine what might be an acceptable error rate, if any, and then have their statistician determine the sample size required to cover that rate. The testing would then confirm the accuracy (not clinical specificity and sensitivity) for that user group on controlled sample testing.

7. What should be the background of these users?

Response: Likely users of the test to be marketed, including a reasonable age range. To reiterate, if it's to be a physician's office test, there's no reason it couldn't be Rx and Waived by using people who normally work in such physicians' offices.

8. What performance criteria (statistical or clinical) should FDA apply to the accuracy threshold for a waived test (e.g., t- test or McNemar test at key decision points, description of performance with confidence intervals at key decision points, use of set performance standards using a receiver operator curve —80%, 90%, 95%, or other—at key decision points, and/or others)?

Response: Simply equivalence between lay and professional users. That is, statistical only. The products' clinical sensitivity and specificity will not change by granting a waiver if the test can be performed with the same accuracy by the lay users.

9. How should FDA define precision for purposes of waiver determination, what types of samples, how many and what types of operators/sites are appropriate? Current CDC recommendation is for 20 participants testing three levels representing appropriate decision points, to be tested at each of three sites by lay users using materials in either artificial and/or real matrices depending on availability and biohazard issues.

Response: Testing 20 samples at three levels representing appropriate decision points by laboratorians and professional users is enough for any test, and at one site, assuming the number of testers and tester diversity is acceptable. In case the question assumes a quantitative result, it should be clarified that the three levels should be a low negative (not zero), a low positive, and a high positive. These three areas will be sufficient to compare the user's results.

10. What performance thresholds should FDA use to determine whether the precision studies are appropriate for waiver status (e.g., ANOVA analysis, use of predefined performance goals such as Tonks' formula, or percent agreement out of total repeat runs)?

Response: This should be up to the statisticians and may be different based on the test, test format, whether it's qualitative or quantitative, and whether it's Rx or OTC.

11. What interference studies are appropriate to establish performance of waived tests (e.g., effects of hemolysis, lipemia, etc.)?

Response: None, this has been done with the 510(k) and is covered in the labeling.

12. What environmental studies or flex (stress) studies are appropriate to establish performance of waived tests (e.g., temperature or humidity stresses, short fills)?

Response: None, this has been done with the 510(k) and is covered in the labeling.

13. What additional studies (if any) should be submitted for evaluation of qualitative tests for waiver?

Response: This was described above, low neg, low pos, and high pos.

14. What additional studies (if any) should be submitted for evaluation of quantitative tests for waiver?

Response: Same as the previous answer.

This concludes responses to the referenced docket. If you have any questions, please feel free to contact me.

Best regards,

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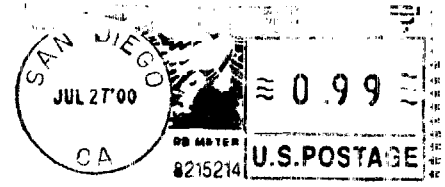

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